Remarks

Currently Claims 22-25 are pending, and each Claim has been amended.

Section 112, First and Second Paragraph Rejections Regarding Use of the Term "Derivative"

Claims 22-25 stand rejected under 35 U.S.C. 112, First and Second Paragraphs, on the basis of the phrase "a pharmaceutically acceptable derivative thereof". The Office Action states that the metes and bounds of the phrase can not be precisely determined.

As described on page 2 of the originally-filed specification, the phrase "pharmaceutically acceptable derivative thereof" is meant to mean any pharmaceutically acceptable salt or solvate of a Cox-2 inhibitor or any other compound, which upon administration to the recipient is capable of providing (directly or indirectly) a Cox-2 inhibitor or an active metabolite or residue thereof. Suitable salts and solvates are described and exemplified on page 6 of the originally-filed specification.

Claims 22-25 have been amended to recite "salt or solvate" rather than "derivative". As such, the Claims more clearly define the invention and more particularly point out the subject matter of the invention. Applicant respectfully submits that the 35 USC 112 rejections based on the term "derivative" have been overcome.

Obviousness-Type Double Patenting Rejections Overcome

Claims 22-25 stand rejected under obviousness-type double patenting in view of Claims 1-4 of U.S. Patent No. 6,759,413 and Claims 19-21 and 24 of U.S. Patent No. 6,831,097. Claims 22 and 24 stand rejected under obviousness-type double patenting in view of Claims 30 and 39 of U.S. Patent No. 6,780,870.

Applicants are filing terminal disclaimers concurrently herewith in compliance with 37 CFR 1.321(c). The terminal disclaimers overcome the obviousness-type double patenting rejections.

Section 112, First Paragraph Rejection Regarding Breadth of Claims

Claims 22-25 stand rejected under 35 U.S.C. 112, First Paragraph. The Office Action states that the specification, while being enabling for the administration of celecoxib or 8-acetyl-3-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine for prokinesia, for lowering esophageal sphincter pressure following administration of celecoxib and for treating post operative ileus following administration of 2-(4-ethoxyphenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, does not reasonably provide enablement for the administration of any compound exhibiting COX-2 inhibiting properties for any disorder ameliorated by a gastroprokinetic. Applicant respectfully traverses this rejection.

Applicant's specification describes *inter alia*, a number of known COX-2 inhibitor compounds, pharmaceutical formulations for such compounds are also known and additional formulations and methods for administration of these compounds are described in the specification at pages 9-11. Applicant has also provided guidance with respect to proper dosing for the treatment of the recited gastroprokinetic conditions.

Further, the specification discloses the *in vivo* effect of several members of the art-recognized class of COX-2 inhibitors on gastric emptying in beagle dogs. The beagle dog is a recognized model for studying gastrointestinal disorders in humans. Evaluating gastric emptying is an art-recognized model for evaluating efficacy for the treatment of NUD. *See*, G. Sarnelli, et al., Am. J. Gastroenterology 98(4):783-788 (2003) and V. Stanghellini, et al., Gastroenterology 110:1036-1042 (1996) (copies enclosed). The data presented in Applicant's specification establishes treatment of the beagle dogs with the COX-2 inhibitors resulted in an enhanced rate of gastric emptying. Enhancement of the rate of gastric emptying is an art-recognized treatment of NUD.

Further, an *in vivo* study of the activity of celecoxib, a COX-2 inhibitor, on lower esophageal sphincter pressure (LESP) in beagle dogs is also reported in the specification. The results showed that celecoxib increased LESP to a similar degree as a known gastroprokinetic agent, cisapride.

Increasing LESP is an art-recognized indicator for efficacy in the treatment of NUD. Thus, Applicant has shown that COX-2 inhibitors both enhance gastric emptying and increase LESP and the results of those test indicate that COX-2 inhibitors as a class, are useful for the treatment of NUD.

The Examiner is reminded that the standard for enablement is whether one skilled in the art can make and use the claimed invention without undue experimentation. Applicant has taught pharmaceutical formulations containing known COX-2 inhibitors, dosing and methods for the administration of those compounds for the treatment of various disorders ameliorated by a gastroprokinetic. The claimed invention is a method of treating NUD by administering a COX-2 inhibitor. By teaching pharmaceutical formulations, dosing and routes of administration, Applicant has taught in the specification how to make and use the claimed invention. Applicant has further established, with relevant, *in vivo* studies, that the compounds have activity for the treatment of NUD. The models used are recognized in the art to correlate to efficacy for NUD.

Various methods for administering COX-2 inhibitors are already known in the art as COX-2 inhibitors are currently marketed in the US and elsewhere for the treatment of other conditions. As such, the skill of those in the art includes knowledge regarding the administration of COX-2 inhibitors. The art also includes knowledge of how to administer known gastroprokinetics, such as cisapride for the treatment of each of the various disorders enumerated in the specification, including NUD.

Accordingly, the guidance and working examples provided by Applicant, the pre-existing knowledge in the art of the administration of COX-2 inhibitors and administration of known gastroprokinetics for the treatment of the enumerated disorders, and the skill of those in the art in the administration of COX-2 inhibitors and gastroprokinetic agents all support Applicant's position that the claims are fully enabled under section 112. Accordingly, withdrawal of this rejection is respectfully requested.

Section 102(a) Rejections

Claims 22 and 24 stand rejected under 35 USC 102(a). The Office Action states that the claims are unpatentable over Morgan, *European J. of Gastroenterology and Hepatology* (Morgan) because Morgan discusses the administration of selective COX-2 inhibitors for reflux esophagitis.

Claims 22 and 24 are both directed to a method of treating NUD (non-ulcerative dyspepsia). Applicant respectfully submits that the Office Action has made no showing or argument that the condition of reflux esophagitis, as mentioned by the reference, would be inclusive of NUD, as claimed. In fact, the Office Action implies that the two conditions are separate conditions. The Morgan reference categorizes reflux esophagitis as an inflammatory condition (page 399, col. 1) while the Office Action states that NUD may or may not be accompanied by inflammation (page 8). Thus, even though the Office Action states that the condition disclosed by the reference and the condition recited in Claims 22 and 24 have an overlapping indication, i.e. inflammation, there is no showing that the conditions are the same.

A finding of anticipation requires that each and every element of a Claim be found, either expressly or inherently described in a single prior art reference. MPEP 2131. Applicant submits that Claims 22 and 24 are both directed to a method of treating NUD (non-ulcerative dyspepsia) rather than reflux esophagitis. Therefore, the reference has not been shown to anticipate Claims 22 or 24 and the rejection under 25 USC 102(a) should be withdrawn.

Section 103(a) Rejections

Claims 22-25 stand rejected under 35 USC 103(a) in view of Morgan. The Office Action states that Morgan teaches COX-2 may have therapeutic potential both against inflammatory conditions such as reflux esophagitis and for gastrointestinal motility disorders. The Office Action concludes that one skilled in the GI art would have been motivated to administer a selective COX-2 inhibitor to treat GI disorders characterized by inflammation and/or motility disturbances in view of Morgan's teaching. Applicant respectfully traverses this rejection.

Applicant respectfully submits that the Examiner has mischaracterized the teaching of Morgan. Morgan does not in fact teach the use of COX-2 inhibitors for the treatment of inflammatory conditions of the GI tract or motility disorders. Morgan is directed toward the effects of NSAIDs in the GI tract. With respect to COX-2 inhibitors and inflammatory conditions of the GI tract, Morgan states only that "it was *proposed* that NSAIDs, particularly selective COX-2-inhibiting NSAIDs, have potential in the treatment of [GERD] and reflux oesophagitis." This is not a teaching of the use of COX-2 inhibitors for GERD and reflux oesophagitis. This is mere speculation; a research proposal offering an invitation to experiment. There is even less connection between COX-2 inhibitors and motility disorders in Morgan. The only reference in Morgan to COX-2 inhibitors in connection with motility disorders states: "Investigating the expression of COX-2 in gastrointestinal motility disorders is also an important research avenue." This is clearly nothing more than an invitation to experiment or suggestion to try COX-2 inhibitors for the treatment of GI motility disorders. This is further evidenced by Table 1, cited by the Examiner. Applicant respectfully points out that after each entry for "COX-2 inhibitor" in table 1 there is a question mark (?), clearly indicating that the authors did not know whether or not a COX-2 inhibitor could be used for that purpose. Lastly, Morgan makes no mention at all of NUD or treatments for NUD. This appears to be acknowledged by the Examiner in that the Office Action does not point to any teaching regarding NUD in Morgan.

The standard for obviousness requires that the Examiner show more than merely a suggestion to try, the Examiner must show a reasonable expectation of success, including some level of predictability. The cited reference fails to disclose or suggest the use of a COX-2 inhibitor for the treatment of NUD. The reference further fails to provide the necessary reasonable expectation of success in the use of a COX-2 inhibitor for the treatment of NUD. Mere speculation and invitations to conduct research are nothing more than suggestions to try and a suggestion to try is insufficient to establish *prime facie* obviousness. *In re Dow Chemical Co., v. American Cyanamid Co.*, 5 USPQ2d 1531 (Fed. Cir. 1988). Accordingly, it is

respectfully submitted that the pending claims are patentable over the cited reference, and withdrawal of this rejection is respectfully requested.

Conclusion

Applicant respectfully submits that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at 919 483-8160, to discuss this case further if desired.

Respectfully submitted,

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THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2003 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 98, No. 4, 2003
ISSN 0002-9270/03/$30.00
doi:10.1016/S0002-9270(03)00053-4

Symptoms Associated With Impaired Gastric Emptying of Solids and Liquids in Functional Dyspepsia

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OBJECTIVES: The relationship between functional dyspepsia and delayed gastric emptying of solids or liquids is still unclear. The aim of the present study was to investigate in dyspeptic patients the prevalence of delayed gastric emptying for solids or for liquids and to investigate the relationship to the dyspepsia symptom pattern.

METHODS: In 392 and 330 patients with functional dyspepsia, the solid and liquid gastric emptying, respectively, was measured using breath tests, and the severity of eight dyspeptic symptoms was scored.

RESULTS: Gastric emptying of solids and liquids were delayed in 23% and 35% of the patients. Multivariate analysis showed that the presence of vomiting and postprandial fullness was associated with delayed solid emptying (OR 2.65, 95% CI = 1.62–4.35 and OR 3.08, 95% CI = 1.28–9.16, respectively). Postprandial fullness was also associated with the risk of delayed liquid emptying when symptom was present (OR 3.5, 95% CI = 1.57–8.68), relevant or severe (OR 2.504, 95% CI = 1.41–4.65), and severe (OR 2.214, 95% CI = 1.34–3.67). Severe early satiety was associated with the risk of delayed liquid emptying (OR 1.902, 95% CI = 1.90–3.30).

CONCLUSIONS: A subset of dyspeptic patients has delayed gastric emptying of solids or of liquids. Delayed gastric emptying of solids was constantly associated with postprandial fullness and with vomiting. Delayed emptying for liquids was also associated with postprandial fullness and with severe early satiety. (Am J Gastroenterol 2003;98:783–788. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Functional dyspepsia is a clinical syndrome characterized by chronic or recurrent upper abdominal pain or discomfort, in the absence of underlying organ disease that can explain the symptoms (1). The symptom complex includes epigastric pain, postprandial fullness, bloating, early satiety, belching, nausea, vomiting, and epigastric burning, and these symptoms are often related to ingestion of a meal (2). The pathophysiology of functional dyspepsia is unknown, and a number of mechanisms have been put forward. These include delayed gastric emptying, hypersensitivity to gastric distension, impaired accommodation to meal, *Helicobacter pylori* infection, abnormal duodenojejunal motility, hypersensitivity to lipids or acid in the duodenum, or central nervous system dysfunction (3–13). Each of these pathophysiologic disturbances can only be demonstrated in subsets of patients, thus establishing the heterogeneity that exists among functional dyspepsia patients (3, 6–14). Similarly, symptom patterns vary greatly among dyspeptic patients, and dividing patients according to the predominant symptom type identifies subgroups with distinct demographic features and functional disturbances (3, 14).

Recent studies have indicated a relationship between specific symptoms and the presence of pathophysiologic mechanisms in functional dyspepsia. The presence of impaired accommodation to a meal is associated with early satiety in dyspeptic patients (7), and the presence of hypersensitivity to gastric distension is associated with symptoms of epigastric pain, belching, and weight loss (8). Several studies have investigated the relationship between delayed gastric emptying of solids and dyspeptic symptom pattern and severity. Depending on the study, the percentage of dyspeptic patients with delayed gastric emptying ranges from 25% to 50% (3, 4, 15–24). Only one study reported an association between symptom pattern and delayed gastric emptying of solids (3). All other studies failed to find a convincing relationship between dyspeptic symptoms and delayed solid gastric emptying (4, 15–24). It is unclear whether this discrepancy relates to patient selection, patient number, type of symptom assessment, cultural or linguistic factors, or the use of less adequate statistical methods (24). The prevalence of delayed gastric emptying of liquids and its relationship to solid emptying rate and to symptoms in functional dyspepsia has received little attention.

The aim of the present study was to investigate in a large series of dyspeptic patients the prevalence of delayed gastric emptying for solids and for liquids and to study the relation between delayed gastric emptying and presence or severity of individual symptoms and the association with demo-

graphic and clinical features. We used an eight-item questionnaire to assess symptom severity, and we used the gastric emptying breath test to assess solid and liquid gastric emptying rate.

MATERIALS AND METHODS

Study Subjects

A total of 392 consecutive patients with functional dyspepsia (117 men and 275 women; age 15–89 yr; mean age 42.9 ± 0.7) participated in this study. All patients fulfilled the Rome II criteria for functional dyspepsia (1). They presented to the outpatient clinic because of epigastric symptoms, and all underwent careful history taking and clinical examination, upper GI endoscopy, routine biochemistry assessment, and upper abdominal ultrasound. Inclusion criteria were the presence of dyspeptic symptoms during at least 12 wk in the last 12 months, in the absence of organic, systemic, or metabolic disease. Dyspeptic symptoms had to be present at least 3 days per week, with two or more symptoms scored as relevant or severe on the symptom questionnaire (see below). Exclusion criteria were the presence of esophagitis, gastric atrophy or erosive gastroduodenal lesions on endoscopy, heartburn as a predominant symptom, a history of peptic ulcer, major abdominal surgery, underlying psychiatric illness, and the use of nonsteroidal anti-inflammatory drugs, steroids, or drugs affecting gastric acid secretion. During upper GI endoscopy, biopsies were taken from the antrum and the corpus to stain with cresyl violet for the presence of *H. pylori*.

All drugs potentially affecting GI motility were discontinued at least 1 wk before the gastric emptying study. The protocol had been previously approved by the Ethics Committee of the University Hospital.

Symptom Questionnaire

Before gastric emptying study, each patient completed a dyspepsia questionnaire, as previously reported (3). The patient was asked to grade the intensity (0–3; 0 = absent, 1 = mild, 2 = relevant, and 3 = severe, interfering with daily activities) of eight different symptoms (epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching, and epigastric burning). Also, the occurrence of weight loss was noted.

Gastric Emptying Studies

Gastric emptying for solids was measured in all patients, using the previously validated ^{14}C-octanoic acid breath test (25). In 330 patients, the gastric emptying for liquids was also determined using the ^{13}C-glycine breath test (26). All studies were carried out in the morning after an overnight fast.

The test meal consisted of 60 g of white bread, one egg, the yolk of which was dosed with 74 kBq of ^{14}C-octanoic acid sodium salt. The meal was ingested within 10 min, immediately followed by 150 ml of water dosed with 100 mg of [1-^{13}C]-glycine in those patients in whom liquid emptying was also assessed. The total caloric value of the test meal was 250 kcal. Breath samples were taken before the meal and at 15-min intervals for a period of 240 min postprandially. Gastric half emptying time ($t_{1/2}$) was calculated as previously described (24, 25).

Data Analysis

The primary end point was the rate of gastric emptying. Delayed emptying was defined as $t_{1/2}$ above the 95% CI in healthy volunteers (>109 min for solids, > 74 min for liquids) (4, 26). Patients were divided into those with normal and those with delayed gastric emptying for solids or for liquids. Then, individual dyspeptic symptoms were analyzed using three possible cutoffs (≥1 *vs* 0; ≥2 *vs* ≤ 1, and 3 *vs* ≤2), and their prevalence was calculated in both subgroups. Rapid emptying was defined as $t_{1/2}$ below the 95% CI in healthy volunteers (<44 min for solids, < 35 min for liquids). Similar analysis was performed.

Statistical Analysis

Age, body weight, height, body mass index (BMI), and $t_{1/2}$ in both patient subgroups were compared using Student *t* test. The prevalence of dyspeptic symptoms, sex distribution, and the presence of *H. pylori* infection in both patient groups were compared by χ^2 testing. Linear regression analysis was used where indicated.

Stepwise multiple logistic regression analysis was used to identify the association between the risk of delayed gastric emptying for solids or for liquids, the presence of dyspeptic symptoms and their severity, and demographic features. *P* values of 0.05 and 0.1 were chosen as cutoff points to enter and exit, respectively, the stepwise procedure. OR with 95% CI were computed. Differences were considered to be significant at the 5% level. All data are given as mean ± SEM. Statistical evaluations were performed using specialized software (SAS, SAS Institute, Cary, NC).

RESULTS

Characteristics of the Patients

Table 1 summarizes the grading of dyspeptic symptoms among the patients. Postprandial fullness and bloating were the most prevalent symptoms, present in 86.7% and 83.4% of the patients, respectively. Nausea (63.8%), epigastric pain (61.5%), early satiety (60.9%), and belching (57.9%) were also frequently reported. Epigastric burning and vomiting were present in 52.8% and 29.1% of the patients, respectively. In 43 of 235 patients, *H. pylori* was demonstrated on gastric biopsies.

Demographic and Symptom Correlates of Delayed Gastric Emptying for Solids

Gastric emptying of solids was significantly delayed in 91 patients (23%); it was normal in 301 patients. There was no significant difference in body weight, height, BMI, or age between patients with delayed and normal gastric emptying (see Table 2). The sex distribution and the prevalence of *H. pylori* infection also did not differ between both groups (Table 2).

Table 1. Frequency of Severity for Each of Eight Symptoms in 392 Patients With Functional Dyspepsia

	0 (Absent)	1 (Mild)	2 (Moderate)	3 (Severe)
Postprandial fullness	52 (13.3)	39 (9.9)	156 (39.8)	145 (37.0)
Bloating	65 (16.6)	39 (9.9)	169 (43.1)	119 (30.4)
Nausea	142 (36.2)	62 (15.8)	113 (28.8)	75 (19.1)
Epigastric pain	151 (38.5)	38 (9.7)	91 (23.2)	112 (28.6)
Early satiety	153 (39.0)	44 (11.2)	96 (24.5)	99 (25.3)
Belching	165 (42.3)	55 (14.1)	123 (31.5)	49 (12.1)
Epigastric burning	185 (47.2)	69 (17.6)	86 (21.9)	52 (13.3)
Vomiting	278 (70.9)	19 (4.8)	32 (8.2)	63 (16.1)

Values are n (row percentage).

The association between symptom severity score and delayed solid emptying was also investigated. The presence of relevant or severe (severity score ≥ 2) symptoms of postprandial fullness (81/91 [delayed solid emptying] *vs* 220/301 [normal], $p < 0.01$), of nausea (58/91 *vs* 130/301, $p < 0.01$), and of vomiting (36/91 *vs* 59/301, $p < 0.01$) was significantly higher in patients with delayed solid emptying (Fig. 1). Similar results were obtained when presence of the symptoms (severity score ≥ 1) was considered: postprandial fullness (55/91 *vs* 254/301, $p < 0.05$), nausea (66/91 *vs* 184/301, $p < 0.05$), and vomiting (72/91 *vs* 72/301, $p < 0.01$) were significantly more prevalent in the subgroup of patients with delayed solid emptying. When symptoms were scored as severe (score = 3), fullness (53/91 *vs* 92/301, $p < 0.01$), bloating (38/91 *vs* 81/301, $p < 0.01$), early satiety (32/91 *vs* 67/301, $p < 0.05$), nausea (25/91 *vs* 50/301, $p < 0.05$), and vomiting (27/91 *vs* 36/301, $p < 0.01$) were all more prevalent in patients with delayed solid emptying.

The prevalence of the other symptoms did not differ between both groups, regardless of the score cutoff level. Weight loss in excess of 5% of the original body weight was also not significantly prevalent in subgroups with delayed and normal solid emptying rate (36/91 *vs* 99/301, ns).

Demographic and Symptomatic Correlates of Delayed Gastric Emptying for Liquids

One hundred seventeen patients (35.4%) had a significantly delayed $t_{1/2}$ for liquids; in 213 subjects liquid emptying was normal. Fifty-one (43.6%) of the patients with delayed liquid emptying also had delayed solid emptying. A significant correlation was found between $t_{1/2}$ for solid gastric emptying and $t_{1/2}$ for liquid gastric emptying ($r = 0.41$, $p < 0.01$).

No significant differences were found between the subgroups with normal or with delayed liquid emptying regarding age (normal: 43.7 ± 0.9 *vs* delayed liquid emptying: 43.8 ± 2.1 yr), weight (64.5 ± 0.8 *vs* 62.9 ± 2.2 kg), length (167 ± 0.5 *vs* 167 ± 1.2 cm), and BMI (23.1 ± 0.3 *vs* 22.4 ± 0.5 kg/m^2). Also, the sex distribution (147/213 men *vs* 87/117 women) and the prevalence of *H. pylori* infection did not differ (28/149 *vs* 4/17).

The presence of relevant or severe (severity score ≥ 2) symptoms of fullness (101/117 [delayed liquid emptying] *vs* 150/213 [normal], $p < 0.01$) and early satiety (68/117 *vs* 95/213, $p < 0.05$) were significantly more prevalent in dyspeptic patients with delayed liquid emptying (Fig. 2). Similarly, when considering presence of symptoms (score ≥ 1), postprandial fullness (111/117 *vs* 175/213, $p < 0.01$) and early satiety (80/117 *vs* 122/213, $p < 0.05$) were significantly more prevalent in the subgroup with delayed liquid emptying. With severe symptom intensity (score = 3), patients with delayed liquid emptying showed significantly higher prevalence of fullness (55/117 *vs* 55/213, $p < 0.01$), bloating (42/117 *vs* 51/213, $p < 0.05$), early satiety (41/117 *vs* 36/213, $p < 0.01$) and vomiting (24/117 *vs* 26/213, $p < 0.05$).

The prevalence of the other symptoms, regardless of the score cutoff level, and weight loss (63/213 *vs* 44/117) did not differ between patients with normal and delayed liquid emptying.

Multivariate Analysis of Pathophysiologic and Symptomatic Correlates of Delayed Gastric Emptying

Stepwise multiple logistic regression analysis was used to identify the association between the risk of delayed gastric emptying for solids or for liquids, demographic features, and symptoms. Age, sex, body weight, height, BMI, and *H. pylori* infection did not influence the risk of delayed gastric emptying either for solids or for liquids.

When considering presence of symptoms (score ≥ 1), relevant or severe symptoms (score ≥ 2), or severe symptoms (score = 3), vomiting and postprandial fullness were consistently and independently associated with the risk of delayed solid emptying (Table 3).

Table 2. Demographic Features in 392 Dyspeptic Patients With or Without Delayed Solid Gastric Emptying

	Age (yr)	Weight (kg)	Length (cm)	BMI (kg/m^2)	Sex (female)	*H. pylori** (positive/negative)
Normal emptying	43 ± 0.9	63.8 ± 0.8	167 ± 0.6	22.7 ± 0.3	208	37/194
Delayed emptying	41 ± 1.7	64.1 ± 1.5	166 ± 1.0	23.0 ± 0.5	67	6/41

Values are mean ± SEM or n.
* *H. pylori* testing was only performed in 235 subjects.

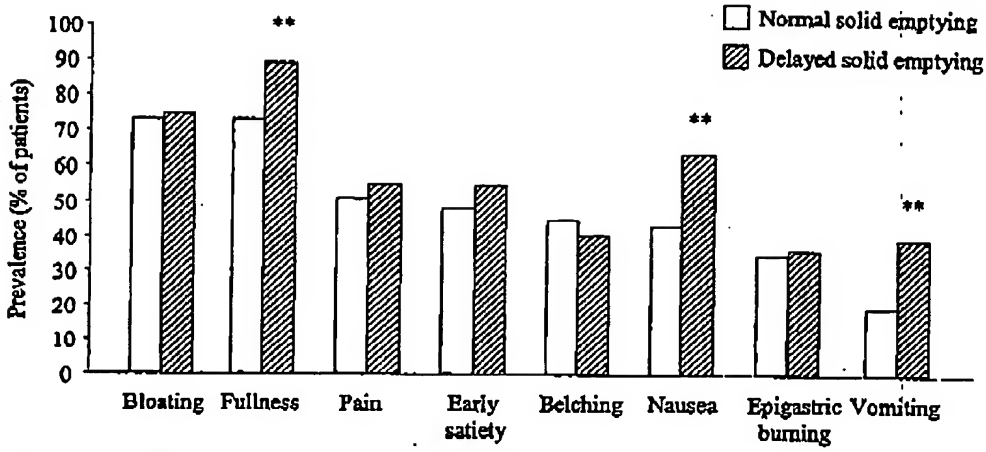

Figure 1. Relationship between symptom severity and solid gastric emptying in patients with functional dyspepsia. The figure shows the percentage of patients grading individual symptoms as relevant or severe (score ≥ 2) in the subgroups with normal or impaired solid gastric emptying. ** $p < 0.01$ *vs* patients with normal emptying.

Postprandial fullness was the only symptom associated with the risk of delayed liquid emptying when considering the presence of symptoms (OR 3.5, 95% CI = 1.57–8.68, $p = 0.004$) and when considering relevant or severe symptoms (OR 2.504, 95% CI = 1.41–4.65, $p = 0.002$). Severe postprandial fullness and severe early satiety were also associated with the risk of delayed liquid emptying (OR 2.214, 95% CI = 1.34–3.67, $p = 0.002$ and OR 1.902, 95% CI = 1.90–3.30, $p = 0.02$, respectively).

Symptomatic Correlates of Rapid Gastric Emptying of Solids or Liquids

Rapid emptying was defined as a $t_{1/2}$ below the 5% CI in healthy volunteers (<44 min for solids, <35 min for liquids).

Solid and liquid emptying were significantly accelerated in 22 and 33 patients, respectively; no significant association between rapid emptying rates and symptoms was observed.

DISCUSSION

Delayed gastric emptying is considered a major pathophysiologic mechanism in functional dyspepsia. Several studies have confirmed that a significant delay in solid gastric emptying rate is present in as many as 50% of patients with functional dyspepsia. However, only one study was able to demonstrate a relationship between delayed solid emptying and the pattern of dyspepsia symptoms (3). We studied the relationship between gastric emptying and dyspepsia symptom pattern in a large series of consecutive patients, using an

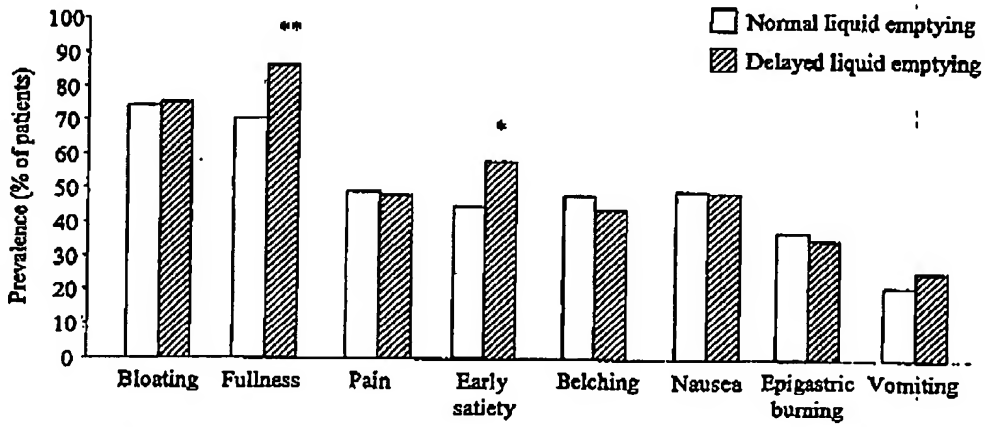

Figure 2. Relationship between symptom severity and liquid gastric emptying in patients with functional dyspepsia. The figure shows the percentage of patients grading individual symptoms as relevant or severe (score ≥ 2) in the subgroups with normal or impaired liquid gastric emptying. * $p < 0.05$, ** $p < 0.01$ *vs* patients with normal emptying.

Table 3. Logistic Regression Analysis of Symptom Severity and the Risk of Delayed Gastric Emptying for Solids in 392 Dyspeptic Patients

	OR	95% CI	p
Presence (score > 0)			
Vomiting	2.65	1.62–4.35	0.0001
Postprandial fullness	3.08	1.28–9.16	0.02
Relevant or severe (score > 1)			
Vomiting	1.99	1.09–3.68	0.02
Postprandial fullness	3.85	1.79–9.09	0.001
Severe (score > 2)			
Vomiting	2.06	1.11–3.78	0.02
Postprandial fullness	2.67	1.60–4.49	0.0002

eight-item questionnaire to assess symptom severity and breath test technology to assess gastric emptying. As glycine does not bind to the solid component of the meal, the dual carbon-labeled breath test allows us to measure gastric emptying rates of liquids and solids independently (26). Delayed gastric emptying for at least one component was found in 41.8% of the patients. Both solids and liquids were delayed in 15.4%; 6.4% had delayed emptying of solids alone and 20% of liquids alone. A multivariate analysis showed that postprandial fullness and vomiting were independently associated with delayed solid emptying, regardless of their severity. Delayed emptying for liquids was significantly associated with postprandial fullness, regardless of cutoff level, and with severe early satiety.

Recently, evidence has accumulated that functional dyspepsia is a heterogeneous disorder, in which different underlying pathophysiologic disturbances are associated with specific symptom patterns. Previously, we demonstrated that impaired accommodation to a meal is associated with early satiety (7) and that hypersensitivity to gastric distension is associated with symptoms of epigastric pain, belching, and weight loss in patients with functional dyspepsia (8). In the current study, we showed that delayed solid emptying is consistently associated with postprandial fullness and vomiting. Our findings confirm and extend the observations by Stanghellini *et al.*, who showed an association of delayed emptying rate of a solid meal with relevant or severe fullness, severe vomiting, and female sex (3). Major differences exist between both studies, such as the language used to express and quantify symptoms, different cultural and alimentary habits in each country, and the use of scintigraphy *versus* the octanoic acid breath test to assess gastric emptying rate. The fact that similar associations between symptoms and delayed gastric emptying were obtained despite these underlying differences confirms the strength of this link between pathophysiologic mechanism and symptom complex.

Several other studies have failed to demonstrate an association between delayed solid emptying and dyspeptic symptoms (4, 15–24). However, these studies evaluated the presence rather than the severity of dyspeptic symptoms, in smaller numbers of patients, and often using less appropriate statistical methods. In contrast to our study, the study by Stanghellini *et al.* also found an association of delayed gastric emptying with female sex and no association with mild or relevant symptoms (3). The authors explained the lack of association of gastric emptying rate with mild symptoms by the overcoming significance of female gender. As the proportion of female patients was similar for both studies, no clear explanation is available for the lack of an association of delayed solid emptying with gender in the present study.

A significant number of our dyspeptic patients showed delayed liquid emptying, which was associated with postprandial fullness, regardless of its severity, and with severe early satiety. As postprandial fullness is also associated with delayed solid emptying, the measurement of liquid emptying besides solid emptying seems to provide relatively little additional pathophysiologic understanding but increases the total prevalence of delayed emptying to 41.8%.

The association of delayed liquid emptying with severe early satiety is surprising, as this symptom has previously been shown to be associated with impaired accommodation of gastric fundus to the meal (7). In patients with impaired accommodation, it has been hypothesized that lack of relaxation of the proximal stomach after a meal induces activation of tension mechanoreceptors in the proximal stomach, thus inducing the symptom of early satiety (7). Although we can not exclude other underlying mechanisms of delayed liquid emptying, such as antral or pyloric functional obstruction, and, in line with the lack of any significant association between accelerated gastric emptying and dyspeptic symptoms, delayed liquid emptying is likely to be associated with pooling of liquids in the proximal stomach. This is probably associated with distention of the proximal stomach, which may also lead to activation of the same tension mechanoreceptors that mediate early satiety (7, 27).

In conclusion, our study showed that delayed gastric emptying for either solids or liquids is present in a large subset of patients with functional dyspepsia. Demographic factors and *H. pylori* status do not differ between patients with normal or with delayed gastric emptying. Delayed gastric emptying of solids is associated with symptoms of postprandial fullness and vomiting, regardless of their severity. Delayed emptying for liquids is associated with postprandial fullness, regardless of its severity, and with early satiety severe enough to interfere with daily activities. Our data add further support to the hypothesis that functional dyspepsia is a heterogeneous disorder, in which different underlying pathophysiologic mechanisms are associated with different symptom profiles.

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Received Apr. 5, 2002; accepted Oct. 10, 2002.

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GASTROENTEROLOGY 1996;110:1036–1042

Risk Indicators of Delayed Gastric Emptying of Solids in Patients With Functional Dyspepsia

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Background & Aims: Although gastric dysmotility and dyspeptic symptoms are often associated, their relationship remains unclear. The aim of this study was to evaluate the relationship between gastric emptying abnormalities and clinical features in functional dyspepsia. *Methods:* In 343 patients with functional dyspepsia, the gastric emptying of solids was measured by a radioisotopic technique and four dyspeptic symptoms (epigastric pain and burning, postprandial fullness, nausea, and vomiting) were measured as absent, mild, relevant, and severe, according to their influence on patients' usual activities. *Results:* Delayed gastric emptying was detected in 33.5% of dyspeptics. Delayed gastric emptying was particularly frequent in patients characterized by female sex, low body weight, presence of relevant and severe postprandial fullness, nausea, vomiting, and absence of relevant and severe epigastric pain. Logistic regression showed that delayed gastric emptying was invariably associated with female sex and with postprandial fullness (odds ratio, 2.34; 95% confidence interval, 1.45–3.75) and vomiting (odds ratio, 4.04; 95% confidence interval, 1.30–12.54) when coded as severe and only postprandial fullness (odds ratio, 3.78; 95% confidence interval, 1.78–8.01) when coded as relevant and severe. *Conclusions:* Female sex, relevant and severe postprandial fullness, and severe vomiting are independently associated with delayed gastric emptying of solids in patients with functional dyspepsia seen in a referral center.

Dyspepsia is a very common syndrome that accounts for about 30% of gastroenterologists' caseloads.[1,2] Patients complaining of long-term or recurrent symptoms that seem to arise from the stomach and proximal small bowel in the absence of organic, metabolic, or systemic diseases are usually classified as having been affected by functional (or idiopathic) dyspepsia.[2–6] This definition helps to differentiate dyspepsia from other gastrointestinal functional syndromes such as irritable bowel syndrome (IBS)[7] and gastroesophageal reflux disease (GERD).[8]

Epigastric pain and discomfort centered in the upper abdomen are the characteristic symptoms of dyspepsia. Discomfort is a term used to describe nonpainful but unpleasant symptoms such as postprandial fullness, bloating, nausea, and vomiting.[6] The existence of patients complaining mainly of epigastric pain and others citing nonpainful discomfort has led researchers to hypothesize about the existence of different subpopulations of dyspeptic patients who have been identified as having ulcer-like and dysmotility-like dyspepsia, respectively.[2,6] The definition of these subpopulations and whether they are characterized by distinctive underlying pathophysiological abnormalities remains to be elucidated.

Gastrointestinal motor abnormalities, *Helicobacter pylori* infection, nonfocal mucosal lesions, hypersensitivity of the afferent nerves of the gut, and psychological disturbances have been said to be involved in the pathogenesis of dyspepsia.[9] Studies of gastrointestinal motility performed by manometric techniques in patients with functional dyspepsia showed a decreased antral contractile response to meal ingestion in up to 50% of the cases,[10–12] whereas abnormalities of small bowel motility are less frequent and seem to characterize patients with autonomic neuropathies[13] or associated IBS.[11,12] Delayed gastric emptying has been found in 10%–64% of these cases.[14–26] Differences in techniques used and populations investigated may account for these impressive differences. Furthermore, the relationship between gastrointestinal motor abnormalities and dyspeptic symptoms has not been clarified. Finally, despite the intuitive feeling of both patients and physicians that the two phenomena may be associated, several studies have failed to identify

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome.

0016-5085/96/$3.00

any correlation.[18,21,23,25,26] Inaccurate definitions of dyspepsia, a limited number of cases, inappropriate symptom questionnaires, or other methodological shortcomings might be responsible for these negative results.

The specific aims of this study were to evaluate whether (1) patients with functional dyspepsia have delayed gastric emptying of solids, (2) gastric emptying abnormalities and dyspeptic symptoms are related, and (3) this relationship is influenced by the symptom scoring technique and/or by other clinical features.

Materials and Methods

Between June 1986 and January 1993, 1037 consecutive dyspeptic patients were referred to our laboratory at the Institute of Internal Medicine and Gastroenterology at the University of Bologna. All the patients underwent careful history taking and physical examination, as well as upper gastrointestinal endoscopy, abdominal ultrasonography, and appropriate hematochemical tests. Only patients who were diagnosed as being affected by chronic functional dyspepsia were included in the study. Inclusion criteria were (1) presence of dyspeptic symptoms lasting for at least 3 months with a global symptom score of at least 3 or greater (see questionnaire below); (2) absence of esophagitis, gastric atrophy, or focal lesions of the gastroduodenal mucosa; (3) absence of organic, systemic, and metabolic diseases, as well as obvious psychiatric illness; and (4) negative history of peptic ulcer, major abdominal surgery, long-term use of steroids or nonsteroidal antiinflammatory drugs, excess alcohol intake, and drug abuse.

The protocol was approved by the University of Bologna S. Orsola hospital ethics committee, and all the subjects gave their fully informed consent.

Symptom Questionnaire

Each patient completed a symptom questionnaire that assessed four symptoms of dyspepsia: epigastric pain and burning, postprandial fullness, nausea, and vomiting. Each symptom was graded 0–3 according to its influence on patients' usual activities: 0, absent; 1, mild (not influencing usual activities); 2, relevant (diverting from but not urging modifications of usual activities); and 3, severe (influencing usual activities markedly enough to urge modifications). The reproducibility of the symptom questionnaire in dyspeptic patients has been previously assessed.[24] Based on previously calculated normal values,[24] total symptom scores ≥ 3 with at least one of the four dyspeptic symptoms graded ≥ 2 were required for entry into the study.

Digestive symptoms other than those typical of dyspepsia were also investigated with appropriate questionnaires. The frequent occurrence of at least three of the classic Manning's criteria (pain relieved by defecation, looser stools at pain onset, more frequent stools at pain onset, visible abdominal distention, feeling of incomplete evacuation, mucus per rectum, and abdominal bloating)[7] was required to diagnose IBS, whereas GERD was defined by the presence of at least one typical symptom (heartburn or acid regurgitation) severe enough to divert the patient from usual activities.[8]

Gastric Emptying

Gastric emptying of the solid components of a mixed meal was studied in each patient using a previously validated radioisotopic technique.[27] Briefly, all drugs potentially affecting gastrointestinal motility were discontinued at least 1 week before the study day. The test meal (638 kcal: 42% carbohydrates, 37% lipids, 21% proteins) was labeled (18.5 MBq of ^{99m}Tc-sulfur colloid) in the solid component (chicken liver) by a previously validated in vitro technique.[28]

Results expressed as the gastric emptying rate (%/min) were calculated as the slope of the rectilinear portion of the gastric emptying curve. Delayed emptying was defined by emptying rates below the lower limit of the sex-specific normal range calculated as mean values ± 2 SD of control subjects (males, 0.42–1.18; females, 0.35–0.93%/min). Lag time values were also calculated as the time between the end of meal ingestion (time 0) and the interception of the rectilinear portion of the curve with the tangent to the peak of the curve and compared with those of control subjects (normal values: males, ≤ 54 minutes; females, ≤ 37 minutes).

Gastric emptying results were compared with those obtained in 50 healthy controls who represented the reference group of our laboratory.

Statistical Analysis

Analysis of variance was used to compare age, weight, or changes vs. ideal body weight in dyspeptic patients and healthy controls. Ideal body weight was estimated according to the Metropolitan Relative Weight Tables.[29] χ^2 analysis was used to compare the distribution of sex in the two populations. Analysis of covariance adjusted for sex, age, and body weight was used to compare gastric emptying rates and lag times in dyspeptic patients and controls. Analysis of variance was also used to evaluate the influence exerted on emptying rates of dyspeptic patients by sex, age, body weight, changes vs. ideal body weight, overlapping IBS and GERD, and grading of symptoms. All these variables were analyzed as dichotomous factors. Linear regression analysis was applied to evaluate the relationship between gastric emptying rates and global symptom scores. Furthermore, individual dyspeptic symptoms were analyzed by considering the three possible cutoffs: (A, ≥ 1 vs. 0; B, ≥ 2 vs. ≤ 1; and C, 3 vs. ≤ 2). Stepwise multiple logistic regression analysis was used to identify the association between the risk of delayed gastric emptying and the above-mentioned possible independent risk indicators. All the possible interactions between these factors were also considered as independent variables. P values of 0.05 and 0.10 were chosen as cutoff points to enter and exit the stepwise procedure. Odds ratios with 95% confidence intervals were computed.

Two tailed P values of <0.05 were accepted as the level of statistical significance. Statistical evaluations were performed

Table 1. Final Diagnosis Formulated After Thorough Investigation in 1057 Patients Referred For Chronic Dyspepsia

Diseases	No.	%
Peptic ulcer	226	21.4
Esophagitis	99	9.4
Biliary tree surgeries	58	5.5
Biliary lithiasis	48	4.5
Atrophic gastritis	46	4.4
Major abdominal surgeries	34	3.2
Gastric malignancies	6	0.6
Other gastrointestinal diseases (chronic liver diseases, pancreatitis, malabsorption, food allergy, etc.)	56	5.3
Diabetes	22	2.1
Metabolic/endocrine diseases (Zollinger–Ellison syndrome, Addison's disease, thyroid diseases, obesity)	33	3.1
Organic/systemic diseases (neoplasms, connective diseases, severe heart or respiratory failure)	28	2.6
Gynecologic diseases	22	2.1
Psychiatric diseases (anorexia nervosa, psychosis, severe anxiety)	36	3.4
Functional (idiopathic) dyspepsia	343	32.5
Total	1057	100

using the statistical software package of SPSS/PC+ (SPSS Inc., Chicago, IL).[50]

Results

The final diagnoses made in the 1057 dyspeptic patients initially investigated are listed in Table 1. A putative cause of dyspepsia was detected in 714 of the patients (68%). The most frequent secondary form of dyspepsia was represented by the peptic ulcer that was found in approximately 20% of the cases. Approximately 10% of the patients had endoscopic evidence of esophagitis. A gastric cancer was disclosed in 6 patients (0.6%). Functional dyspepsia was diagnosed in 343 patients (32%) who were the object of further analysis. Of these, 96 (28%) had overlapping IBS and 108 (32%) overlapping GERD.

Patients and controls were significantly different in sex, age, and body weight. Females were more prevalent among dyspeptics (150 males and 193 females) compared with controls (30 males and 30 females; $P = 0.031$). Patients were also older (39.1 ± 12.4 years, mean ± SD) than controls (34.5 ± 12.4 years; $F = 5.99$; $P = 0.014$). Finally, patients had lower body weight (63.1 ± 12.1 kg) than controls (67.3 ± 11.2; $F = 5.43$; $P = 0.020$) but presented similar percentage changes vs. ideal body weight (respectively, −2.4 ± 12.5, 0.2 ± 9.7). Table 2 summarizes the prevalence and grading of dyspeptic symptoms. Among patients, postprandial fullness and epigastric pain accounted for 94% and 84%, respectively, of frequently reported symptoms. Both symptoms were more often reported as relevant or severe. Nausea and vomiting were less frequent and severe, being reported as absent or mild by 72% and 90%, respectively, of the cases.

Dyspeptic patients had gastric emptying lag times (12.47 ± 17.04 minutes; mean ± SD) similar to those of controls (15.32 ± 15.43) but lower emptying rates (patients, 0.51 ± 0.24%/min; controls, 0.67 ± 0.18; $F = 14.63$; $P = 0.0001$). Gastric emptying was delayed in 24.7% of male patients and in 40.4% of female patients. On average, females had emptying rates (0.46 ± 0.22) lower than males (0.59 ± 0.23; $F = 28.65$; $P = 0.0001$). Similarly, patients with body weight lower than ideal body weight ($n = 192$) had lower emptying rates (0.47 ± 0.22) than those with body weight equal to or greater than ideal body weight ($n = 151$; 0.57 ± 0.25; $F = 18.79$; $P = 0.0001$). Gastric emptying was not influenced by age or by the presence of overlapping IBS and GERD.

A significant, although poor, negative relationship was found between total global scores and emptying rates ($r = -0.20$; $P = 0.0001$). However, when multiple logistic regression analysis was applied to test the influence of demographic features (i.e., age, sex, and body weight) and the global symptom score on the risk of gastric dysmotility, only the female sex turned out to be significantly associated with delayed gastric emptying (odds ratio, 2.07; 95% confidence interval, 1.30–3.31; $P = 0.0024$).

We also investigated the association between individual symptom grading and gastric dysmotility. Patients complaining of relevant and severe (score ≥2) postprandial fullness, nausea, and vomiting presented decreased emptying rates (respectively, 0.48 ± 0.22, 0.44 ± 0.21, and 0.41 ± 0.19) compared with patients with absent or mild (<2) forms of the corrispective symptoms (0.65 ± 0.25, $F = 32.99$, $P = 0.0001$; 0.54 ± 0.24, $F = 11.46$, $P = 0.0007$; 0.52 ± 0.24, $F = 6.78$, $P = 0.0092$).

Table 2. Frequency of Intensity Scoring For Each of Four Symptom Complaints in 343 Patients With Functional Dyspepsia

	0 (Absent)	1 (Mild)	2 (Relevant)	3 (Severe)
Epigastric pain	55 (16)	102 (30)	127 (37)	59 (17)
Postprandial fullness	22 (6)	47 (14)	145 (42)	129 (38)
Nausea	134 (39)	113 (33)	67 (20)	29 (8)
Vomiting	250 (73)	60 (17)	18 (5)	15 (4)

NOTE. Numbers in parentheses represent row percentages.

Table 3. Logistic Regression Model Testing For an Influence of Demographic Data and Symptom Scoring on Delayed Gastric Emptying of Solids in 343 Patients With Functional Dyspepsia

	Odds ratio	95% confidence intervals	P value
A			
Female sex Age <40 yr BW < IBW Epigastric pain ≥1 Postprandial fullness ≥1 Nausea ≥1 Vomiting ≥1	2.03	(1.27–3.25)	0.0033
B			
Female sex Age <40 yr BW < IBW Epigastric pain ≥2 Postprandial fullness ≥2 Nausea ≥2 Vomiting ≥2	1.82	(1.13–2.96)	0.014
	3.78	(1.78–8.01)	0.001
C			
Female sex Age <40 yr BW < IBW Epigastric pain = 3 Postprandial fullness = 3 Nausea = 3 Vomiting = 3	1.66	(1.15–3.02)	0.0119
	2.34	(1.45–3.75)	0.005
	4.04	(1.30–12.54)	0.0157

NOTE. Symptom scoring is coded as: A, presence vs. absence of symptoms; B, presence of relevant and severe symptoms vs. the absence or presence of mild symptoms; and C, presence of severe symptoms vs. the absence or presence of mild and relevant symptoms.
BW, body weight; IBW, ideal body weight.

Patients with relevant and severe epigastric pain, conversely, showed accelerated emptying (0.55 ± 0.24) compared with patients with an absent or a mild (<2) grade of the symptom (0.47 ± 0.23; $F = 5.18$; $P = 0.0036$). When the influence of the presence or absence of dyspeptic symptoms on emptying rates was analyzed (score 0 vs. score ≥1), only postprandial fullness appeared to be associated with delayed emptying (score 0, 0.62 ± 0.28; score ≥1, 0.51 ± 0.23; $F = 5.18$; $P = 0.0228$).

Logistic regression analysis showed that female sex, relevant and severe postprandial fullness, and severe vomiting were the only factors independently associated with delayed gastric emptying (Table 3). Female sex was associated with delayed gastric emptying, regardless of symptom coding. When symptoms coded as severe (score, 3) were selected, both postprandial fullness and vomiting turned out to be significantly associated, whereas when selecting the symptom code as relevant and severe (score, ≥2), only postprandial fullness was significantly associated. Evaluation of all the interactions between the factors potentially influencing gastric emptying did not show any significant further effect.

Discussion

This study confirms that gastric emptying of the solid components of caloric mixed meals is delayed in patients with chronic functional dyspepsia seen in a referral center. It also shows that, in this population, female sex, relevant and severe postprandial fullness, and severe vomiting are independently associated with delayed gastric emptying.

The number and type of associated diseases diagnosed in dyspeptic patients seen in our center are not substantially different from those of other groups previously described in Western countries.[31,32] Also, the extent of overlap between dyspepsia and other digestive functional syndromes of about 30% is similar to that reported by others with respect to overlapping IBS[32] but slightly lower with respect to overlapping GERD reported in up to 56% of the cases.[33] Different definitions of dyspepsia and GERD and inclusion of mild forms of the syndromes in these studies may account for these differences. Our patients mainly complained of postprandial fullness, a symptom suggestive of a digestive motor disorder. This confirms the majority of previous reports describing dysmotility-like symptoms as the most common complaint of dyspeptic patients seen by both gastroenterologists[34] and general practitioners.[35]

Gastric emptying of solids has been almost invariably found to be delayed in dyspeptic patients,[14–17,20,21,23,24,36] but the influence of demographic and clinical features on this parameter has not been thoroughly investigated. In the present study, female sex, low body weight, relevant and severe postprandial fullness, nausea, and vomiting as well as the absence of relevant and severe epigastric pain and burning were all found to be associated with delayed gastric emptying. However, the logistic regression analysis showed that only female sex, relevant and severe postprandial fullness, and severe vomiting are independent risk indicators of delayed emptying.

Some studies have already pointed out that gastric emptying abnormalities are more frequent in female than male dyspeptic patients.[18,21,26,36] Systematic studies on the influence of gender on gastric emptying have consistently shown that both premenopausal women and postmenopausal women on estrogen and progesterone replacement therapy have a delayed gastric emptying of solids compared with men,[37,38] but the mechanisms through which females have a higher risk of deranged gastric motility than males remain unclear.

Research in the field of functional dyspepsia is particu-

larly intriguing because, in the absence of specific pathophysiological markers, the diagnosis can be solely based on symptom questionnaires. International panels of clinical investigators agreed that dyspeptic patients may fall into distinct symptom subgroups that may indicate different underlying etiologies.[2,6] These subgroups included patients with typical ulcer symptoms (ulcer-like dyspepsia), patients with symptoms suggestive of gastrointestinal motor abnormalities (dysmotility-like dyspepsia), patients with symptoms suggestive of gastroesophageal reflux (reflux-like dyspepsia) who may also be classified as having GERD,[6] and patients with symptoms that do not fall into any of the above categories (unspecified dyspepsia).

Talley et al. tested a questionnaire designed to distinguish these different dyspepsia subgroups both in the general population[59] and in patients undergoing upper gastrointestinal endoscopy in a tertiary referral center.[32] They concluded that dyspepsia subgroups, as classified in these studies, had "little clinical utility" and were "an inappropriate way of classifying dyspepsia."[32] However, the results of these studies are difficult to interpret because the questionnaire adopted had two major shortcomings. First, it originated from a restrictive definition of dyspepsia focused on the presence of pain (i.e., 10 of the 15 symptoms on the questionnaire were variants of pain, and the presence of pain was requested for inclusion in all the different subgroups of dyspepsia). Second, it did not quantitate the severity of symptoms but only described their presence or absence. The simple perception of digestive symptoms is of limited clinical value because they are extremely frequent in the general population and among individuals who do not seek medical advice.[6] Similarly, in patients with GERD, the relevance of heartburn and regurgitation, but not their mere presence, has been shown to be of predictive value for pathological gastroesophageal reflux.[6] We adopted a multiple point adjectival scale that allows us to ascertain the frequency and the impact on usual activities of 4 dyspeptic symptoms that is easy to understand for the patient and also highly reproducible.[24,40]

The clinical utility of this questionnaire could probably be increased by asking more specific questions. For instance, epigastric burning pain localized in the upper portion of the epigastrium could be more specific for GERD than a nonburning painful sensation vaguely localized in the central part of the upper abdomen. Also, the postprandial duration of fullness could be at least as important as the severity of the symptom in predicting the presence of gastric stasis. Distinguishing early satiety from postprandial fullness could help to differentiate those patients whose main pathophysiological abnormality is a defective gastric accomodation. However, these hypotheses require verification in well-designed studies with an appropriate number of throughly selected patients.

The relationship between dyspeptic symptoms and digestive motor functions is particularly controversial. A significant, although weak, negative correlation between gastric emptying rates and global symptom scores was detected in our study, suggesting that patients with more severe complaints also have lower emptying velocities. However, multivariate analysis showed that the global symptom score is not associated with gastric emptying rates as an independent variable and that its effect is overcome by gender. By analyzing individual symptom scoring, we observed that patients complaining of relevant and severe postprandial fullness or severe vomiting have an increased risk of delayed gastric emptying compared with patients with different symptom profiles. To the best of our knowledge, only one study adopted a similar (although more complex) scoring system.[18] Despite the small number of patients involved, a borderline significant correlation was found between belching and delayed gastric emptying when the symptom scores (but not the simple presence or absence of symptoms) were analyzed. By contrast, the majority of investigations that failed to identify a correlation between gastric emptying abnormalities and dyspeptic symptoms did not use any quantitative analysis of individual symptoms but simply analyzed the presence or absence of symptoms,[21,36] clusters of symptoms,[25,26] or global symptom scores.[20,36] In keeping with these studies, our findings showed that neither the symptoms or clusters of symptoms considered as a dichotomous variable and coded as present or absent nor the global symptom score had any predictive value for delayed gastric emptying. In addition to the different questionnaires adopted, other variances with previous reports include the use of a low caloric test meal,[23] the inclusion of secondary forms of dyspepsia[19,23,25] or of symptoms suggestive of digestive syndromes other than dyspepsia,[16,21,23,25,26] and the small number of cases investigated.[19,21,23,26]

Indeed, previous studies support the existence of a correlation between dyspeptic symptoms and gastric motor abnormalities. In a double-blind, crossover, placebo-controlled trial of the prokinetic cisapride in patients with symptomatic gastroparesis, we observed a significant positive relationship between the degree of improvement of gastric emptying and the degree of improvement of the symptoms limited to the active treatment arm.[41] In keeping with these findings, Jian et al. described a

greater gain induced by cisapride on symptoms suggestive of motor disorders in patients with delayed gastric emptying than in those with normal gastric motility.[20] A significant, although weak, correlation between severity of symptoms and gastric emptying times had also been found in diabetic patients.[42] More recently, it has been shown that the presence of *H. pylori* infection and delayed gastric emptying identify two subpopulations among dyspeptic patients[24,43] and that these subgroups present different symptom profiles characterized by the prevalence of epigastric pain and postprandial fullness, respectively.[24] Finally, stimulation of mechanoreceptors experimentally obtained by inflating rubber balloons either in the stomach or in the proximal small bowel has been shown to induce a rather monotonous and reproducible individual response with the perception of sensations suggestive of motor derangements such as fullness, pressure, and nausea.[44]

The correlation between dyspeptic symptoms and delayed gastric emptying is not a direct one, as indicated by the absence of any detectable abnormality of gastric emptying of solids in many of the dyspeptic patients we observed. Factors other than digestive motor disorders are probably involved in the complex mechanism leading to visceral perception, including sensitization of receptors other than mechanoreceptors, visceral hypersensitivity due to abnormal neural activity of afferent fibers, and abnormal perception of peripheral signals at the central level.[6]

In conclusion, the present study shows that gastric emptying of solids is delayed in patients with functional dyspepsia and that female sex, postprandial fullness severe enough to influence the usual activities, and vomiting severe enough to urge changes in the usual activities are independently associated with delayed gastric emptying. Analysis of the intensity of digestive symptoms, not only of their presence, is mandatory when investigating the relationship between visceral perception and potentially associated pathophysiological factors. The present study was performed in a highly selected group of patients seen in a referral center. Generalizability of these results regarding other dyspeptic patients commonly seen by general practitioners or gastroenterolgists remains to be established.

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Received August 31, 1995. Accepted November 28, 1995.

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The authors thank Dr. Vay Liang W. Go of UCLA for reviewing the manuscript and Rosa Elena Garcia for skillful assistance in preparation of the manuscript.